REMARKS

The claims have been amended to simplify prosecution. The limitations of claim 62 have been inserted into claim 60. The limitations of claim 70 have been inserted into claim 68. Claim 77 has been amended to depend from claim 60 rather than from canceled claim 56. Thus, no new matter has been added and entry of the amendment is respectfully requested.

Applicants note the lack of SEQ. ID. NO. on page 36; this has been corrected by amendment.

The Rejection of Claims 54-77 Under 35 U.S.C. § 101

All claims were rejected under this section as putatively lacking utility. The Office takes the position that the protein is useless because antibodies raised against it would not necessarily serve to detect cancer cells. The reasoning of the Office is that the evidence in the specification regarding expression in cancer cells which is focused on production of mRNA does not predict the production of the corresponding protein in these cells. The Office cites documents which report specific instances in which either the levels of mRNA and the encoded protein do not correspond or in which under certain circumstances mRNA may be present but no protein is detected.

Applicants respectfully submit that the occurrence of individual instances of lack of protein when mRNA is present do not contravene the general understanding in the art, sworn to in Dr. Hubert's declaration, currently of record, that:

> [W]ith rare exceptions, expression of a polynucleotide, particularly mRNA with an open reading frame and a Kozak consensus sequence for

translation initiation, is predictive of expression of the corresponding protein.

No evidence has been offered by the Office that there are a substantial number of cases where there is no protein produced when mRNA is shown to be present, nor that there is an expectation in art that no protein produced when mRNA is shown to be present. This may be an instance where the exceptions prove the rule. It is well-understood that there are such exceptions; nevertheless, as stated by Dr. Hubert under oath, the general and scientifically accepted principle is that the presence of mRNA does predict the presence of protein.

In a recent article in *Proteomics* (2001) 1:1303-1319, Oh, J.M.C., *et al.*,described databases compiled to provide an overall picture of the correlation of protein production with mRNA production. Apparently, this overall correlation has not yet been done or has not been published. Evidence of the type suggested by the Office is simply anecdotal. The Office might consider the possibility that the majority of cases, where protein and mRNA are both present do not warrant a publication merely corroborating the expected concomitant occurrence of these substances. Moreover, to the extent that Oh *et al.* do correlate mRNA and protein, they find that where mRNA is present, the corresponding protein is as well.

Further, it should be noted that "correlation" can be interpreted in at least two ways - whether there is a direct relationship between the *amounts* of mRNA and protein and whether there is a relationship with regard to the *presence* of mRNA and protein. Clearly, it is much rarer that mRNA would be present with no protein at all, than are instances where the relative amounts are not consistent among various mRNA's and various proteins.

Applicants recognize that they have already argued that Fu, *et al.*, is an exception; however, the response by the Office does not support the proposition that a failure to find protein

when mRNA is present is a general rule. The Office cites Alberts, *et al.*, for the teaching that "translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated." The Examiner has kindly provided a copy of the cited document. However, the cited document does not state this proposition at all. It merely says that the RNA can become degraded when DNA synthesis stops, presumably because histones are no longer present. So, Alberts does not actually support the position of the Office. The disclosure of Alberts actually supports applicant's position since the degraded mRNA would not be detectable by Northern blot either.

The Office further cites Shantz and Pegg, which are said to teach that ornithine decarboxylase is highly regulated at the level of translation and that translation of the mRNA is dependent on the secondary structure and the availability of eIF-4E. What this paper does not say is that anything other than the levels of ornithine decarboxylase are thus regulated. The paper does not say that mRNA will be detected even though ornithine decarboxylase is not made, which is the position taken by the Office with regard to the PHELIX protein.

The Office then cites McLean and Hill for the teaching that P-glycoprotein can be overexpressed in CHO cells without any concomitant overexpression of the P-glycoprotein mRNA. This hardly shows that mRNA will be detected in the absence of the production of the protein; it may show there is more protein than there is mRNA detectable.

In short, none of these cited documents describe any other single instance where mRNA would be detected but no protein would be found. The Office fails to provide any evidence that the putative lack of correlation between mRNA detection and protein detection is a general, scientifically accepted rule.

In summary, the citation of one isolated instance, one that does not involve the PHELIX protein, in which mRNA detection is not accompanied by protein, is insufficient to support the general proposition, proposed by the Office, that the production of mRNA is not predictive of protein production as well, or is not predictive in this case. The value of mRNA detection as an indication of protein production has been substantiated on the record already in the Declaration of Dr. Hubert.

Enclosed herewith is additional testimony from an expert in the field establishing that mRNA production is an art-recognized method of ascertaining that protein is produced. As stated in the Declaration of Dr. Challita-Eid, it is general knowledge in molecular biology that, *with rare exceptions*, production of mRNA does predict the production of the corresponding protein and this is particularly true for mRNA with an open reading frame and a Kozak consensus sequence for translation initiation (See paragraph 6.)

Paragraph 7 of the Declaration points out the features of the PHELIX mRNA which show that it has the required Kozak consensus sequence. Paragraph 8 explains why Northern blot technique to detect mRNA is used in preference to Western blotting which detects protein directly. Paragraph 9 provides the results of Declarant's experience that those practicing the art routinely use Northern blot as an index of ultimate protein expression.

A particular interest may be the discussion in paragraph 11 indicating that the supposed "lack of correlation" of mRNA and protein expression refers to the levels of those expressions, not the complete absence of protein when mRNA has been detected.

As stated in paragraph 13, the article cited by the Office, Fu, L., *et al.,* is a highly unusual exception to the generality that where there is mRNA, there is also protein. Further, the Declaration explains in paragraphs 15-16 explain why the demonstration that has already been

made of production of the PHELIX protein in 293 cells is relevant to the production of this protein in tumor cells.

In light of Dr. Challita-Eid's declaration, and in the absence of any documentation showing that the exceptional case noted by the Office has any generality, it is believed that that much of the rejection which is based on an asserted lack of correlation between Northern blot results and protein production may be withdrawn.

Aside from this, antibodies which have been demonstrated as capable of detecting PHELIX proteins, have uses other than detection of cancer. As the Office acknowledges, these antibodies are useful in studying the role of production of this protein in cancer progression. Should the protein not be expressed, or cease to be expressed, in cancer cells where the message has been shown to be present, the availability of such antibodies to the protein permit revelation of this fact. This effectively forecloses what might otherwise be explored as a possible target, for example, for cancer vaccines. Such information is just as useful as a positive result as it prevents further investigation in a fruitless line of research.

For the reasons set forth above, the rejection of the claims for lack of utility may properly be withdrawn.

The Rejection of Claims 68-69 and 71-72 Under 35 U.S.C. § 112, Para. 1 - Written Description

This basis for rejection is moot in view of the amendments to the claims. The limitations of claim 70, *which claim was not included in this rejection*, have been inserted into claim 68, from which claim 69 depends. Claims 71-72 have been cancelled Accordingly, these claims are no longer subject to the rejection.

The Rejection Under 35 U.S.C. § 112, First Paragraph, of Claims 54-77 - Lack of Enablement

This basis for rejection is grounded in the same rationale as the utility rejection under 35 U.S.C. § 101 discussed above. Applicants' response to this basis for rejection is identical to that set forth with regard to the utility rejection.

The Rejection of Claims 56-70 and 77 - Enablement

These claims have been amended. Claim 60 is directed to the specified peptide at residues 140-154 of SEQ. ID. NO: 2 which has been demonstrated as immunogenic, as acknowledged by the Office. However, the Office raises doubts that the antibodies raised are specific to the protein of SEQ. ID. NO: 2 and raises the possibility that crossreaction with other proteins is possible. This is a characteristic of all antibodies, and following the logic of the Office, there would be no possible use for any antibody preparation at all. The Office is entirely correct that the antibodies raised by the claimed fragment might crossreact with other proteins; however, a distinction can be drawn experimentally by testing immunoreactivity in the presence and absence of the peptide used to elicit the immune response. Because crossreactive proteins are generally weaker binders than the protein from which the peptide was derived, the presence of this peptide would interfere with binding of the antibody to the crossreactive proteins, but would interfere less strongly with binding of the antibodies to the protein target. Thus, there is clearly a way to distinguish the desired interaction from interactions which are artifacts.

Applicants note that this argument is not applied to claims 54-55; this is entirely proper, but applicants point out that the same issues of crossreactivity would arise with respect to antibodies raised by the full-length protein. The reason this should not be an issue is that is it

well understood that some crossreactivity may occur; however, this can be distinguished, for example, by the methods set forth above.

Applicants further note that the claims subject to this rejection have been limited to the subject fragment which has been shown to be immunogenic (claims 60-61) or to an isolated polypeptide that is at least 90% identical to the amino acid sequence of SEQ. ID. NO: 2 over its entire length and where the polypeptide is recognized by an antibody that binds a PHELIX protein having SEQ. ID. NO: 2. These latter claims (68-69) take advantage of the crossreactivity noted by the Office. It provides for the possibility that similar proteins due to allelic variations, for example, may exist in cancer cells.

It is believed that the foregoing is responsive to that portion of the rejection which is applicable to the remaining claims. There should be no further issue of scope with regard to the fragments as discussed on pages 11-12 of the Office action or the scope issues discussed on pages 13-14, bridging paragraph. Further, the discussion of immunogenicity of short peptide sequences on page 14 is believed irrelevant in view of the amendment to the claims. Similarly, due to the cancellation of claims directed to eliciting CTL's, the discussion on page 15 is also moot.

The Rejection of Claims 68-69 and 70-72 Under 35 U.S.C. § 112, Paragraph 1 - Scope

It is believed this rejection is mooted by amendment as the rejection was not applied to claim 70, the scope of which has been incorporated into independent claim 68.

CONCLUSION

The claims have been amended to focus the invention. Applicants appreciate the apparent recognition that the claimed subject matter is free of the art. The rejections for utility/lack of enablement are believed in error as the art recognizes the predictive nature of mRNA expression with regard to the presence of protein and in any event, antibodies raised to the protein would be useful even if the protein itself is not expressed in cancer cells. Accordingly, the pending claims, claims 54-55, 60-62, 68-69 and 74-77 are believed in a position for allowance and passage of these claims to issue is respectfully requested.

Applicants again express their appreciation for the time and thought provided at the interview by the Examiner. It is believed that the foregoing arguments are consistent with the discussion. Should there remain matters to be resolved in order to pass this application to allowance, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 511582002700.

Respectfully submitted,

Dated: June 13, 2002

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the paragraph on page 35, line 36 through page 36, line 5, as follows:

In order to generate antibody reagents that specifically bind to PHELIX, a 15 mer peptide was designed from the PHELIX coding region. Specifically, the peptide HSSKEKLRRERIKYC (positions 140-154 of SEQ. ID. NO: 2) was conjugated to keyhole limpet hemocyanin (KLH) and used to immunize a rabbit. Rabbit serum was tested for reactivity with a recombinant PHELIX protein, as described in Example 6, below. The rabbit polyclonal antiserum demonstrated specifically for PHELIX and may therefore be useful for assessing the expression of PHELIX in patient samples.

In the Claims:

60. (Amended) An isolated polypeptide of at least 15 contiguous amino acids of the sequence shown in SEQ ID NO: 2, wherein the polypeptide is recognized by an antibody that specifically binds a PHELIX protein having the amino acid sequence of SEQ ID NO: 2, and which comprises amino acid residues 140-154 of SEQ ID NO: 2.

68. (Amended) An isolated polypeptide that is at least 90% identical to the amino acid sequence of SEQ ID NO: 2 over the entire length of SEQ ID NO: 2, wherein the polypeptide is recognized by an antibody that specifically binds a PHELIX protein having the amino acid sequence of SEQ ID NO: 2 that is a conservative substitution mutant of a protein having the amino acid sequence of SEQ ID NO: 2.

77. (Amended) A composition for eliciting formation of antibodies directed to a cell that expresses a PHELIX protein, the composition comprising:

(a) an immunogenic portion of a PHELIX protein according to claim [56] 60; and

(b) a pharmaceutically acceptable carrier.